Impaired visual and spatial reversal learning in brain-damaged rats: Additional components of the "general learning system" of the rodent brain

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Based on earlier lesion studies, it was reasoned that the components of the rodent's "general learning system" (an ensemble of brain structures essential for normal acquisition of a wide variety of laboratory tasks) could roughly be identified by determining which lesion placements within the rat brain would lead to defective acquisition of a spatial discrimination and its reversal as well as a visual discrimination and its reversal. Of the 29 cortical and subcortical sites investigated to date, only 9 qualify as components of the general learning system—pontine reticular formation, median raphe, interpeduncular nucleus and central tegmentum, substantia nigra, red nucleus, parafascicular nucleus, lateral thalamus, ventrolateral thalamus, and globus pallidus. It is proposed that these 9 brain regions constitute a major part of an organized nervous substratum mediating "anticipatory sets."

In a previous report (Thompson, 1982a), it was proposed that the components of the "general learning system" (an ensemble of neural structures conceived to be essential for normal acquisition of a wide variety of laboratory tasks) of the rodent brain could roughly be identified by determining which structures of the rat brain, when selectively damaged, would induce significant learning deficits on the following four tasks: A simple spatial (vestibular-proprioceptive-kinesthetic) discrimination habit and its reversal, and a simple visual (white-black) discrimination habit and its reversal. This proposal was based upon earlier lesion studies that showed that those brain structures involved in the *retention* of both visual and vestibular-proprioceptive-kinesthetic discrimination tasks were also likely to be involved in the retention of such tasks as a complex maze, latchbox problems, and avoidance responses (Thompson, 1982b).

The initial study (Thompson, 1982a), which examined 11 cortical and subcortical sites (frontal cortex, parietal cortex, occipital cortex, anterior cingulate cortex, posterior cingulate cortex, rostral caudoputamen, dorsal hippocampus, mammillary bodies, mediodorsal thalamic nucleus, parafascicular nucleus, and substantia nigra), disclosed that only bilateral lesions in the region of the occipital cortex, the parafascicular nucleus, or the substantia nigra

significantly impaired acquisition of all four discrimination tasks. When these results were compared with other findings, it was concluded that the regions of the parafascicular nucleus and substantia nigra are likely components of the general learning system, but that the occipital cortex is not.¹

In the current experiment, 12 additional regions of the rat brain were investigated in relation to their possible inclusion within the general learning system. Bilateral damage to any one of these regions (olfactory bulb, globus pallidus, ventral hippocampus, rostral medial forebrain bundle, anterior thalamus, lateral thalamus, ventrolateral thalamus, ventromedial thalamus, red nucleus, interpeduncular nucleus and central tegmentum, median raphe, and pontine reticular formation) has already been shown to impede acquisition and reversal of a position habit formed in a single-unit T-maze (Thompson, Note 1). It remains to be shown whether comparable lesions to these structures will likewise impede acquisition and reversal of a white-black discrimination habit. Any one of the foregoing brain sites found to be critical for acquisition of these visual tasks would, according to the argument introduced above, qualify as a component of the general learning system.

METHOD

Subjects and Surgery

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Under deep chloral-hydrate anesthesia (250 mg/kg), male Sprague-Dawley albino rats, 80-120 days old, were subjected to bilateral olfactory bulbectomy, bilateral subcortical lesions, or sham operations. Bulbectomy was accomplished by aspiration,

and subcortical injuries were made stereotactically by passing a constant anodal current (1.6-2.5 mA) for 5-10 sec through an implanted stainless steel electrode with 1.0-2.0 mm of the tip exposed. The size and locus of the lesions of the various experimental groups were intended to be comparable to those suffered by the corresponding groups investigated earlier in connection with acquisition of the spatial discrimination tasks. The sham-operated controls underwent anesthetization, shaving of hair over the cranium, exposure of the skull, and suturing without any further treatment.

The animals were usually housed, two per cage, in medium-size wire cages containing a constant supply of food pellets and water. Throughout the recovery period, the animals were handled for approximately 5 min on every 3rd day. Preliminary training was instituted 2-3 weeks postsurgically. On the day prior to preliminary training, the vibrissae of each animal were shaved (see Thompson, 1982a).

Apparatus

A two-choice Thompson-Bryant discrimination box, utilizing the motive of escape-avoidance of footshock, was employed (see Thompson, 1978a). Two pairs of stimulus cards mounted on wooden blocks were used in the apparatus. One pair (two medium-gray cards) was employed in training the animals to displace a card in order to gain access to the goalbox. The second pair consisted of a white card and a black card.

All parts of the grid floor of the apparatus were connected to an alternating-current source regulated by a Variac. The intensity of footshock ranged from 1.2 to 1.8 mA.

Procedure

Preliminary Training

Following habituation to the goalbox, each animal was trained to run from the startbox and through the choice chamber, displace one of the gray cards blocking the windows, and enter the goalbox in order to escape from (or avoid) footshock. The rat was first placed in the startbox and the startbox door was raised. Failure to leave the startbox within 5 sec was followed by brief footshocks until the animal entered the choice chamber. If the rat failed to enter the goalbox from the choice chamber within 5 sec, additional footshocks were administered. (During the early phase of training, the cards were positioned at an angle from the window, allowing a space for the rat to enter the goalbox.) Training was continued until the rat readily displaced the cards on three successive trials without the aid of footshock.

Original Learning

Formal training on the white(positive)-black(negative) discrimination began 24 h after the completion of preliminary training. An approach response to the unlocked white card admitted the animal to the goalbox, whereas an approach response to the adjacent locked black card (error) was punished by footshock. If an error was committed, the animal was forced to respond to the white card in order to gain entrance to the goalbox. An error was defined as an approach response to the black card that brought the animal's forefeet in contact with the charged grid section that extended 8.0 cm in front of the black card. The position of the white (and black) card was switched from the right to the left window in a sequence mixed with single- and double-alternation runs.² Eight trials were usually given each day, with an intertrial interval of 50-75 sec. The criterion of learning consisted of either a "perfect" (Grant, 1946) or "near-perfect" (Runnells, Thompson, & Runnells, 1968) run of correct responses having a probability of occurrence of less than .05, followed by at least 75% correct responding in the subsequent block of 8 trials given on the next day. In a few cases, the criterion was not reached within 100 trials. The animals involved received

no further training on the original problem and were not required to learn the reversal problem.

The specific training procedure was as follows: The rat was placed in the startbox, and the startbox door was raised. Failure to leave the startbox within 5 sec was followed by brief footshocks. No further footshocks were given unless the rat made an error or failed to make a choice within 5 sec. The animal was allowed to remain in the goalbox for 10 sec, after which it was transferred to a restraining cage to await the next trial. The animals were usually run in squads of two.

Reversal Learning

On the day following the attainment of the criterion of learning on the original problem, the animals began training on the reversal problem—black card positive versus white card negative. The training procedure was the same as that described in Original Learning. Postoperative training was terminated when the animal reached the criterion of learning or when the animal received 100 trials.

Histology

Each brain-damaged animal was killed with an overdose of chloral hydrate, its vascular system perfused with normal saline followed by 10% Formalin, and the brain removed and stored in 10% Formalin for 2-4 days. Each brain having subcortical lesions was then blocked, frozen, and sectioned frontally at 90 μ . Every fourth section through the lesioned area was retained and subsequently photographed at 12 $\times$ by using the section as a negative film in an enlarger.

Measurements of Performance

Performance measures consisted of both trials to criterion and initial errors to criterion. A third measure (total errors to criterion) was also included because it was not uncommon for an animal to commit multiple errors within a given trial. Multiple errors occurred when the animal retreated from the charged grid section and then approached the negative card a second (third, fourth, etc.) time, each approach response resulting in footshock. Therefore, total errors to criterion involved the sum of approaches to the negative card that resulted in footshock.

Since several brain-damaged groups were significantly inferior to the controls in original learning of the white-black problem, a "reversal learning deficit" cannot reasonably be inferred from the finding that a given experimental group was significantly inferior to the controls in learning the reversal problem. However, a reversal learning deficit would be apparent if a given brain-damage group committed proportionately more errors (or required proportionately more trials) in learning the reversal problem, as opposed to the original problem, than the controls. To accomplish this, individual "savings scores" were computed for each measure of performance according to the following formula: [(original learning score - reversal learning score)/original learning score] $\times$ 100.

RESULTS

Original and Reversal Learning

Table 1 shows the three measures of performance on the original problem and the reversal problem for all groups. These data will be discussed in terms of the site of brain damage.

Control Group

All sham-operated control subjects learned the original problem within 40 trials. On the reversal problem, the poorest control animal learned in 72

Table 1
Mean Learning Scores on the Original and Reversal Problems for All Groups

Group	Original Problem				Reversal Problem			
	N	Trials	Initial Errors	Total Errors	N	Trials	Initial Errors	Total Errors
Control	9	25.7	14.6	21.6	9	42.9	25.0	37.1
Olfactory Bulb	5	24.6	13.4	18.4	5	36.2	19.4	28.8
Anterior Thalamus	6	21.7	9.8*	15.8*	6	33.2	20.0	40.3
Ventromedial Thalamus	5	29.8	12.4	20.6	5	40.6	23.8	48.4*
Lateral Thalamus	8	66.0*	31.8*	42.6*	5	70.1*	36.5*	54.0*
Ventrolateral Thalamus	5	42.4*	19.6	31.0	5	67.0*	35.4	45.2
Globus Pallidus	6	47.5*	23.7*	44.0*	6	65.8*	34.0	65.2*
Ventral Hippocampus	5	30.4	16.4	23.4	5	38.4	24.8	37.8
Medial Forebrain Bundle	7	27.6	13.9	22.7	7	31.3	19.4	34.7
Red Nucleus	6	76.7*	36.8*	47.7*	3	89.0*	51.0*	57.7*
Interped Nucleus/Cent Tegmentum	4	67.0*	31.0*	43.5*	3	100.0*	45.0*	50.0*
Median Raphe	3	100.0*	47.0*	56.0*				
Pontine Reticular Formation	5	71.2*	25.0*	34.6*	3	74.7	39.3*	62.0*

Note—Interped Nucleus/Cent Tegmentum = interpeduncular nucleus and central tegmentum.

*Differed from the controls at least at the .05 level.

trials. Based on the Wilcoxon test for paired replicates, the reversal problem was significantly more difficult to master than the original problem in terms of all three measures of performance ($ps < .01$).

Bulbectomy Group

The olfactory bulbs were completely ablated in five rats. In all cases, there was slight damage to the frontal poles of the cerebrum. This group tended to learn the original and reversal problems faster than the controls did, but the Mann-Whitney U test disclosed that the differences in trial and error scores were far from being statistically significant.

Thalamic Groups

Anterior region. Five of the six animals of this group suffered varying amounts of damage to the anteromedial nucleus (Figure 1). In four of these cases, the mammillothalamic tract was severed bilaterally. Other injured structures included the dorsal hypothalamus and the medioventral, anterodorsal, anteroventral, mediodorsal, and reticular thalamic nuclei. The sixth animal of this group had a lesion largely confined to the anterodorsal and anteroventral thalamic nuclei.

In terms of both initial and total errors to criterion, this group learned the original problem significantly *faster* than the controls did. The differences in reversal learning scores, however, were far from statistical significance.

Ventromedial region. All five animals of this group sustained some damage to the ventromedial, submedial, and central medial thalamic nuclei. One had a lesion largely confined to the ventromedial thalamus (Figure 2A), two had dorsally placed lesions that extensively damaged the mediodorsal thalamic nucleus (Figure 2B), and two had ventrally placed lesions that invaded the dorsal hypothalamus (Figure 2C).

Although performance on the original problem was not remarkably different from that of the controls, this group did show a significant deficit in learning the reversal problem in terms of total errors to criterion.

Lateral region. Eight animals suffered bilateral injuries to the lateral thalamic complex. In all cases, the lesions extensively damaged the lateral dorsal and lateral posterior (pulvinar) thalamic nuclei. The dorsal hippocampus was slightly injured in two cases, the medial portion of the lateral geniculate nucleus

Figure 1. Photographs of three unstained sections showing an anterior thalamic lesion in one animal.

Figure 2. Photographs of unstained sections (from three animals) showing lesions confined to (A) or invading (B and C) the ventromedial thalamus.

Figure 3. Photographs of three unstained sections showing a lateral thalamic lesion in one animal that failed to learn the original discrimination.

(pars dorsalis) in two cases, and the rostral pre-tectum in six cases. The posterior, ventrobasal, ventrolateral, and central lateral thalamic nuclei were either spared or slightly invaded.

Three of the eight animals were unable to learn the original problem within 100 trials (Figure 3). Of the five animals that successfully learned the original problem, four reached the criterion of learning on the reversal problem within 100 trials (Figure 4). As a group, these animals were significantly inferior to the controls in learning both the original and reversal problems.

Ventrolateral region. Five animals received relatively discrete lesions within the ventrolateral thalamic nucleus. In all cases, the overlying lateral thalamic complex was invaded, but the ventrobasal complex was largely spared (Figure 5).

As a group, these animals required significantly more trials to master the original problem and the reversal problem than did the controls.

Other Subcortical Groups

Globus pallidus. Six rats sustained multiple lesions of the globus pallidus (Figure 6). In all cases, the adjacent caudoputamen was damaged, but the internal capsule was invaded in only two cases.

As a group, these animals were significantly re-

Figure 4. Photographs of three unstained sections showing a lateral thalamic lesion in one animal that learned both visual problems.

Figure 5. Photographs of three unstained sections showing a ventrolateral thalamic lesion in one animal.

Figure 6. Photographs of three unstained sections showing a pallidal lesion in one animal.

tarded in learning both the original and reversal problems.

Ventral hippocampus. Five animals were subjected to bilateral electrolytic lesions of the ventral hippocampus (Figure 7A). In two cases, the subiculum was also damaged bilaterally, and in the remaining three cases, there was extensive damage to the entorhinal cortex.

These animals were not significantly different from the controls in acquiring either the original habit or the reversal habit.

Rostral medial forebrain bundle. All seven rats of this group suffered injuries to the medial forebrain bundle. In five subjects, the lesions were centered at the level of the anterior commissure (Figure 7B). The remaining two animals had more posteriorly placed lesions at the level of the anterior thalamus (Figure 7C).

This group was virtually indistinguishable from the controls in original learning. Although they tended to learn the reversal problem faster than the controls, the differences in performance measures fell short of statistical significance.

Red nucleus region. Six animals sustained relatively small lesions of the rubral area and surrounding midbrain reticular formation (Figure 8). Three succeeded in mastering the original problem within

Figure 7. Photographs of unstained sections (from three animals) showing lesions to the ventral hippocampus (A) and rostral medial forebrain bundle (B and C).

Figure 8. Photographs of three unstained sections showing a rubral lesion in an animal that failed to learn the original discrimination.

Figure 9. Photographs of three unstained sections showing a lesion of the interpeduncular nucleus and central tegmentum in an animal that failed to learn the reversal problem.

100 trials, but only one of these was able to master the reversal problem within 100 trials.

Interpeduncular nucleus and central tegmentum. Four rats had midline lesions that damaged varying amounts of the interpeduncular nucleus and overlying central tegmentum (Figure 9). Three were able to learn the original problem within 72 trials, but none of these succeeded in learning the reversal problem within 100 trials.

Median raphe region. The three rats with midline lesions that encroached significantly upon the median raphe were unable to learn the original problem within 100 trials (Figure 10).

Pontine reticular formation. Five rats suffered relatively discrete lesions within the pontine reticular formation (Figure 11). Three of these animals were able to learn the original problem within 69 trials, but only two were able to learn the reversal problem within 100 trials.

Reversal Learning Deficit

As described earlier, a "reversal learning deficit" would be indicated by the finding that a given brain-damaged group committed proportionately more errors (or required proportionately more trials) in learning the reversal problem, as opposed to the original problem, than did the controls. This com-

Figure 10. Photographs of three unstained sections showing a lesion to the median raphe in an animal that failed to learn the original discrimination.

Escape-Avoidance Behavior

Figure 11. Photographs of three unstained sections showing a pontine reticular formation lesion in an animal that failed to learn the reversal problem.

parison could be accomplished by computing individual savings scores for each measure of performance. Table 2 presents the means of these savings scores for all groups. It will be noted that only one of the 12 brain-damaged groups achieved significantly poorer savings scores than did the controls on at least one measure of performance. This group had lesions in the region of the anterior thalamus. A marginally significant deficit in total error savings scores ($p = .10$) occurred in the group with ventromedial thalamic lesions.

During both original learning and reversal learning, the majority of brain-damaged animals readily entered the choice chamber from the startbox and responded to one of the stimulus cards either without footshock or with the application of one or two footshocks. However, three rats with pallidal, one with anterior thalamic, one with medial forebrain bundle, and one with interpeduncular-nuclear/central-tegmental lesions frequently required more than the usual number of footshocks to force escape responses in the apparatus. It should be noted that the animals requiring multiple footshocks to force escape responses were not the slowest learners in their respective groups.

A more frequently observed "aberrant" escape-avoidance response consisted of extremely rapid running from the startbox toward the goalbox. This appeared in 4 of the control animals and in 23 of the brain-damaged (1 with olfactory bulbectomy, 2 with ventral hippocampal, 2 with medial forebrain bundle, 5 with lateral thalamic, 3 with ventrolateral thalamic, 4 with rubral, 1 with interpeduncular-nuclear/central-tegmental, 2 with raphe, and 3 with pontine reticular formation lesions) animals. (In an effort to reduce running speed, a delay of 10-20 sec was routinely imposed between inserting the animal into the startbox and raising the startbox door.)

General Health

All brain-damaged (and control) animals appeared quite healthy and alert at the time preliminary training was begun. The three animals (two with pallidal and one with rubral lesions) that showed eating and drinking disturbances beyond the 3rd postsurgical day gradually recovered these behaviors when provided with sweetened wet mash in the home cage.

Table 2
Mean Savings Scores for All Groups

Group	N	Trials		Initial Errors		Total Errors	
		Mean	Range	Mean	Range	Mean	Range
Control	9	-72.2	-158 to 16	-71.2	-143 to -29	-73.9	-142 to 6
Olfactory Bulb	5	-65.8	-147 to 24	-48.8	-82 to 6	-57.6	-81 to -25
Anterior Thalamus	6	-66.8	-173 to -5	-123.3*	-220 to -44	-215.2*	-614 to -61
Ventromedial Thalamus	5	-38.0	-124 to 4	-93.0	-182 to -36	-155.6	-293 to -62
Lateral Thalamus	5	-67.4	-142 to 6	-76.5	-117 to -9	-78.0	-155 to -4
Ventrolateral Thalamus	5	-71.6	-180 to -20	-87.6	-158 to -44	-59.4	-153 to -18
Globus Pallidus	6	-43.0	-89 to 11	-45.4	-78 to -23	-44.3	-87 to -15
Ventral Hippocampus	5	-26.8	-72 to 4	-53.4	-86 to -25	-61.8	-87 to -32
Medial Forebrain Bundle	7	-17.0	-93 to 30	-38.7	-100 to 10	-68.9	-200 to 19
Red Nucleus	3	-78.3	-117 to -27	-74.3	-135 to -31	-34.7	-60 to -9
Interped Nucleus/Cent Tegmentum	3	-85.0	-122 to -41	-81.7	-123 to -30	-18.7	-40 to 9
Pontine Reticular Formation	3	-42.3	-47 to -33	-69.3	-77 to -55	-56.0	-70 to -35

Note—Interped Nucleus/Cent Tegmentum = interpeduncular nucleus and central tegmentum.

*Differed from the controls at least at the .05 level.

DISCUSSION

General Findings

The basic findings of this study were that bilateral lesions in the region of the lateral thalamic complex, the ventrolateral thalamus, the globus pallidus, the red nucleus, the interpeduncular nucleus and central tegmentum, the median raphe, or the pontine reticular formation significantly impaired both original learning and reversal learning of a white-black discrimination problem in the rat. On the other hand, rats with bilateral lesions of the olfactory bulbs, the ventral hippocampus, the rostral medial forebrain bundle, the anterior thalamus, or the ventromedial thalamus were unimpaired in original learning and, except for the last lesion, in reversal learning of the brightness discrimination.

It was not surprising that pallidal, rubral, interpeduncular-nuclear/central-tegmental, median raphe, or pontine reticular formation lesions retarded acquisition of a visual discrimination habit. Normal rats trained on visual discrimination problems and subsequently subjected to any one of the foregoing lesions often earn postoperative relearning scores that are greater than the corresponding preoperative learning scores (Thompson, 1978a).

Contrariwise, it was totally unexpected that damage to either the lateral thalamic complex (LD-LP) or the ventrolateral thalamus (VL) would impede acquisition of the two visual discrimination tasks. In my laboratory, transoperative retention of either brightness- or pattern-discrimination habits has not been found to be compromised by lesions within LD, LP, and/or VL (Thompson, 1978a). In light of this pattern of results, it seems very likely that LD, LP, and VL are concerned with the formation of new visual discrimination habits rather than being concerned with the expression of previously learned visual discrimination habits.³ Collateral support for this conclusion comes from the findings that LP lesions impair acquisition (Legg & Cowey, 1977) but not retention (Hughes, 1977) of brightness-discrimination habits. However, the results of McDaniel and Thomas (1978) stand in opposition to this conclusion. These investigators failed to note a deficit in either original learning or reversal learning of a white-black discrimination in rats prepared with LP lesions.

These opposing findings of McDaniel and Thomas (1978) are difficult to explain, but one possible interpretation is offered here. It appears that the LP lesions investigated in the McDaniel and Thomas study were posterior to those examined in the Legg and Cowey (1979) study and in the current study. Since the results of the current study suggest that a lateral thalamic focus for brightness-discrimination learning deficits embraces VL, LD, and LP, it would

follow that a caudal LP lesion (damage to the fringe of the thalamic focus) would be less apt to produce a learning defect than would a rostral LP lesion (damage within the thalamic focus). An experiment comparing rostral and caudal LP lesions on white-black discrimination learning is needed to test this notion.

According to an earlier study (Thompson, 1978a), damage to the olfactory bulbs, the rostral medial forebrain bundle, the anterior thalamus, or the ventromedial thalamus does not appreciably affect retention of brightness- or pattern-discrimination habits in the rat. Similar negative findings have been observed in rats prepared with ventral hippocampal damage (Thompson, Note 1). In view of the results of the present experiment, it would appear that the foregoing structures are likewise not critical for acquisition of visual discrimination habits.

Investigators have, on occasion, reported that a given brain-damaged group will learn a visual discrimination habit significantly faster than will controls. Such a facilitative effect has recently been observed by Sara and David-Remacle (1981) in hippocampally lesioned rats and by Thompson (1982a) in mammillary-body-lesioned rats. The present study disclosed that anterior-thalamic-lesioned rats learn a white-black discrimination problem faster than do controls. Since these brain-damaged animals made an average of 3.5 errors over the first eight training trials, it is unlikely that the anterior thalamic lesions had somehow induced an appreciable preference for the white card over the black card. However, the control animals of the current study committed an average of 5.0 errors over the first eight training trials. This difference in 1st-day error scores between the anterior thalamic and control groups is marginally significant ($p = .10$, Mann-Whitney U test). Such an outcome suggests that the rapid learning by the anterior thalamic group may be due to the fact that the lesions diminished the rats' initial preference for the black card. Interestingly, visual cortical lesions may have similar effects (Krechevsky, 1936).

Several brain-damaged groups of the current experiment were found to be significantly retarded in learning the reversal problem, but this result alone does not necessarily reflect a "reversal deficit." However, evidence for the latter would be indicated by the finding that a given brain-damaged group earned significantly poorer savings scores than the controls did. As shown in Table 2, the only groups that exhibited a significant (or marginally significant) reversal deficit had lesions to either the anterior thalamus or ventromedial thalamus. (Unfortunately, termination of training on the original or reversal problems in those animals receiving lateral thalamic, rubral, interpeduncular-nuclear/central-tegmental, median raphe, or pontine reticular formation lesions

made it impossible to obtain adequate assessment of the savings scores earned by the corresponding brain-damaged groups.) It is interesting to note that the study related to the present one (Thompson, 1982a) reported reversal deficits arising from either posterior cingulate, mammillary body, mediodorsal thalamic, or nigral lesions. Considering that all of the ventromedial-thalamic-lesioned rats of the current experiment suffered interruption of the mammillo-thalamic tract, it becomes clear that a major division of the Papez circuit may be involved in visual discrimination reversal learning—namely, the mammillary bodies, mammillothalamic tract, anterior thalamus, and posterior cingulate cortex. The inclusion of the hippocampus would, of course, complete the circuit, except that neither dorsal hippocampal (Thompson, 1982a) nor ventral hippocampal (current study) lesions were found to produce a reversal deficit. This is a conspicuous omission, especially in view of the fact that other investigators have reported impairments in visual discrimination reversal learning in the presence of hippocampal system damage (Becker & Olton, 1980; Samuels, 1972; Silveira & Kimble, 1968). The claim that the use of the escape-avoidance motive in the current study is responsible for this omission fails to account for the positive effects arising from lesions to other elements of the Papez circuit. Although lesion size may be a factor (Samuels, 1972), it must be pointed out that the dorsal and ventral hippocampal lesions examined in my laboratory are sufficient to elicit significant deficits in spatial reversal learning (Thompson, 1981, Note 1). In any event, visual (and spatial) discrimination reversal deficits do seem to be linked to interference with the mammillary-thalamic-cingulate complex. It remains to be seen whether reversal deficits in the presence of nonlimbic lesions (e.g., mediodorsal thalamus and substantia nigra) are the consequences of altering the activities of this complex.

General Learning System

Additional Components

As discussed in an earlier report (Thompson, 1982a), there is a reasonable basis for the belief that those lesion placements impairing acquisition of both spatial (vestibular-proprioceptive-kinesthetic) and visual discrimination habits in the rat will roughly define the components of the rodent's general learning system (GLS) of the brain. Of the 11 brain sites examined in the earlier report, only the parafascicular and nigral regions were considered to be likely components of the GLS.

The present investigation attempted to extend these findings by examining 12 additional brain regions, each of which had previously been found to be implicated in acquisition of both a position habit

and its reversal (Thompson, Note 1). Seven of these regions were found to be critical for acquisition of a white-black discrimination and its reversal. These regions include the globus pallidus, the lateral thalamic complex, the ventrolateral thalamus, the red nucleus, the interpeduncular nucleus and central tegmentum, the median raphe, and the pontine reticular formation.

In light of earlier findings, it appears quite reasonable to include the regions of the globus pallidus, the red nucleus, the interpeduncular nucleus and central tegmentum, the median raphe, and the pontine reticular formation within the GLS of the rodent brain. Rats with bilateral damage to any one of these regions have been reported to exhibit relearning disturbances (errors to relearn postoperatively being greater, in many cases, than errors to learn preoperatively) on a variety of tasks, including visual discriminations (Thompson, 1976), an inclined plane discrimination (Thompson, Arabie, & Sisk, 1976), a three-cul maze (Thompson, 1974), and latchbox problems (Spiliotis & Thompson, 1973; Thompson, Gates, & Gross, 1979). Severe retention losses on active- and/or passive-avoidance responses have also been observed in rats prepared with any one of these lesions (Thompson, 1978b).

The decision to include the lateral thalamic complex and ventrolateral thalamus within the GLS is made with some degree of hesitancy. Aside from the studies reviewed earlier on the effects of LP lesions on visual discrimination learning, virtually no information on the significance of VL, LD, or LP in acquisition of laboratory tasks exists in the animal literature. A small body of information does exist on the effects of lesions to these thalamic nuclei on retention of certain learned habits, but such information may be irrelevant (e.g., LP lesions impair acquisition, but not retention, of a brightness-discrimination habit) unless relearning disturbances (negative savings scores) are obtained.

It is interesting to note that relearning disturbances on a three-cul maze habit (Thompson, 1974), an inclined plane discrimination task (Thompson et al., 1976), and certain latchbox problems (Thompson et al., 1979) have indeed been observed to arise from lateral or ventrolateral thalamic lesions in rats. However, while rats with VL lesions have been reported to earn negative savings scores on an active avoidance response (Thompson, 1978b), rats with lateral thalamic lesions rapidly relearn this response (Olton & Isaacson, 1967; Thompson, 1978b). Passive-avoidance habits appear to be spared following VL, LD, or LP lesions (Thompson, 1978b).

At this juncture, it is noteworthy to mention that patients with VL lesions are apt to show disturbances in recent memory for verbal material if the lesions are located on the left side (Blumetti & Modesti, 1980; Krayenbühl, Siegfried, Kohenof, & Yasargil,

Figure 12. Schematic drawing of a parasagittal section of the rat brain showing the relative positions of the 29 sites where lesions were separately placed. Encircled capital letters refer to those sites included within the GLS—selective lesions to those sites produced learning deficits on both visual and spatial discrimination tasks. (Although lesions to the occipital cortex also produced spatial and visual discrimination learning losses, this structure was excluded from the GLS.) Capital letters that are not encircled refer to those sites associated with spatial discrimination learning deficits only. Lowercase letters refer to those sites associated with no spatial discrimination learning deficits. Abbreviations: A = anterior thalamus; AC = anterior cingulate cortex; amy = amygdaloid complex; DH = dorsal hippocampus; DM = dorsomedial thalamus; FR = lateral frontal cortex; GP = globus pallidus; IC = interpeduncular nucleus and central tegmentum; L = lateral thalamic complex; MB = mammillary bodies; MFB = rostral medial forebrain bundle; mrf = dorsal midbrain reticular formation; np = nucleus posterior thalami; OCC = occipital cortex; OLF = olfactory bulb; P = pontine reticular formation; PAR = parietal cortex; PC = posterior cingulate cortex; PF = parafascicular nucleus; R = median raphe; RCP = rostral caudoputamen; RN = red nucleus; sc = superior colliculus; SN = substantia nigra; vb = ventrobasal thalamic complex; VH = ventral hippocampus; VL = ventrolateral thalamus; VM = ventromedial thalamus; zi = zona incerta.

1965; Ojemann, Hoyenga, & Ward, 1971) and disturbances in recent memory for nonverbal material if the lesions are located on the right side (Blumetti & Modesti, 1980). Electrical stimulation of the lateral thalamic complex has been reported to produce similar effects (Fedio & Van Buren, 1975; Ojemann & Fedio, 1968).

Figure 12 summarizes the research findings to date on the quest for those structures composing the GLS of the rodent brain. Of the 29 brain sites examined with lesions, 23 were found to be implicated in original and reversal learning of a position habit.⁴ Of these, only 10 were also found to be implicated in original and reversal learning of a white-black discrimination. Excluding the occipital cortex¹ from this number leaves a total of nine components currently making up the GLS (the abbreviations of these components are encircled in Figure 12).

Anatomical and Functional Considerations

In the initial study of the rodent's GLS (Thompson, 1982a), it was concluded that the nigral-parafascicular-

striatal complex constitutes a major part of that ensemble of brain structures conceived to be essential for normal acquisition of a wide variety of laboratory tasks. It was also mentioned that this complex may play an "arousal-activation" and/or a "motor control" role in the learning process.

Although the results of the current experiment have led to an appreciable expansion of the GLS, it is remarkable that most of the additional components are anatomically related to the nigral-parafascicular-striatal complex. The globus pallidus, of course, is a major subdivision of the striatum and contributes many of its axons to the substantia nigra (Carter & Fibiger, 1978). The raphe nuclei appear to have connections with all components of the nigral-parafascicular-striatal complex (Comans & Snow, 1981; Miller, Richardson, Fibiger, & McLennan, 1975; Reubi & Emson, 1978), whereas the pontine reticular formation seems to contribute fibers to only the last two components (Comans & Snow, 1981; Lynch, Smith, & Robertson, 1973). Direct connections of the red nucleus and the interpeduncular nucleus and central tegmentum with the nigral-parafascicular-striatal complex have not been documented in the rat, but it is noteworthy to mention that striatal afferents from the interpeduncular nucleus and the retrorubral nucleus have been observed in the cat (Vandermaelen, Kocsis, & Kitai, 1978). With respect to the ventrolateral thalamus, both Carter and Fibiger (1978) and Clavier, Atmadja, and Fibiger (1976) have shown that the basal part of this nucleus is the recipient of nigral as well as entopeduncular efferents. [The rubrothalamic tract may also terminate within the ventrolateral nucleus (Condé & Condé, 1980).] Finally, while direct connections between the lateral thalamus and the nigral-parafascicular-striatal complex have not been fully established, it is important to note that lesions of the lateral thalamus may, under certain conditions, alter catecholamine activity within the substantia nigra (Hirayama, Gabra-Sanders, Mendelow, & Gillingham, 1982).

In light of the foregoing anatomical considerations, it is conceivable that the various components of the GLS combine to serve a common function. Such a function would undoubtedly be a broad one, covering many aspects of motor control, arousal-activation states, and cognitive processes. That this would seem to be the case is indicated by the fact that the neostriatum alone appears to play a role in sensory, motor, and cognitive processes (Divac & Öberg, 1979).

Before considering this broad function, it is essential to point out that most of the components of the GLS have been implicated in retention of previously learned responses (Thompson, 1982b), as well as in that process dealing with the "focusing of attention" (Hassler, 1978). Thus, a major portion of the GLS appears to have functional significance

for learning, retention, and attention. (It should not be surprising that the neural substrates underlying learning, retention, and attention should share common elements when it is considered that virtually any kind of learning activity depends upon retention and that learning must certainly require the engagement of a selective attention mechanism.)

In discussing the inadequacies of various theoretical attempts to explain the anatomical basis of learning in general and the conditioned response in particular, Sperry (1955) introduced a factor that has long been recognized to play an essential role in the acquisition and expression of learned responses. This factor is the "anticipatory set," or "expectancy." For Sperry, this anticipatory set, which develops through training, exerts an organizing effect on the brain on both the sensory and motor sides—it mobilizes those facilitatory and inhibitory processes that allow the relevant stimulus impulses to release the appropriate motor response. I propose that the neural substratum for anticipatory sets includes the GLS shown in Figure 12.

There are a number of reasons for linking anticipatory sets with the GLS. First of all, the current composition of the GLS, which includes portions of the basal ganglia, thalamus, limbic midbrain area, and brainstem reticular formation, clearly contains those anatomical and functional features that could support anticipatory sets as well as mobilize those excitatory and inhibitory processes impinging upon other brain regions.

Second, it is likely that the morphological substratum underlying one kind of anticipatory set (involving maze learning) would share a number of common elements with that underlying another kind of anticipatory set (involving visual learning). As already demonstrated, the GLS appears to be made up of those brain sites having the distinguishing feature of participating in the acquisition of an assortment of learned responses.

Third, the findings on "assimilation of rhythms"—the appearance during the intertrial interval of brain activity normally evoked by the conditioned stimulus—and related "endogenous" processes (John, 1967, 1972) can readily be interpreted as neural correlates of anticipatory sets.⁵ Of interest here is the fact that these "assimilated rhythms arise earliest, are most marked, and persist longest in nonsensory-specific structures" (John, 1967, p. 327). At the present time, the GLS contains at least two structures (pontine reticular formation and parafascicular nucleus) that belong to the "nonsensory-specific" systems of the brain.

Finally, neurophysiological studies (Olds, Disterhoft, Segal, Kornblith, & Hirsh, 1972) on the identification of those units of the brain that exhibit conditioned responses with the shortest latencies have revealed "learning units" within the pontine reticular formation, the parafascicular nucleus, and the lateral

thalamic complex. Each of these structures is a component of the GLS.

Final Considerations

There is little doubt that learning involves the engagement of many functional systems of the brain. On these grounds alone, the GLS can be viewed as no more than an aggregate of discrete anatomical foci, each contributing in a specialized way to the learning process. For example, the interpeduncular nucleus and central tegmentum and the median raphe may simply play a role in behavioral inhibition, the nigrostriatal complex may function in arousal-activation processes, the pontine reticular formation and red nucleus may contribute to motor control, the parafascicular nucleus may be concerned with escape-avoidance responses, and the lateral and ventrolateral thalamic nuclei may be in the service of sensorimotor integration. Although this molecular approach may be the correct one to pursue, the remarkable degree of interconnectivity among the various components of the GLS suggests the presence of an organized substratum having a unitary function.

Throughout this study, it has been assumed that cell destruction at the site of the lesion is responsible for any ensuing learning losses. This assumption, of course, must be seriously questioned in light of the possibility that fiber damage and secondary brain changes may also have contributed to the learning losses (Schoenfeld & Hamilton, 1977). How, then, does one interpret the data in relation to the GLS in the absence of any assessment of these inadvertent lesion effects on learning? First of all, it will be recalled that 29 different brain regions were canvassed with lesions. Of these, only 9 (excluding the occipital cortex) were associated with significant learning losses on both visual and spatial discrimination tasks. It may be inferred, therefore, that these 9 brain regions, which are included within the GLS, are potentially more involved in the general learning process than are the remaining 20 brain regions that have been excluded from the GLS.

Other shortcomings related to the current series of experiments on the identification of the GLS have already been discussed (Thompson, 1982a). Despite these, the demonstration of a correspondence between presumably nonspecific learning deficits and the destruction of a relatively localized anatomical complex does shed new light on the brain mechanisms underlying learning and memory.

REFERENCE NOTE

1. Thompson, R. Unpublished observations, 1981.

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NOTES

1. Bilateral damage to the occipital cortex has been reported to have little effect on original learning of either a tactile discrimination (Finger, Cohen, & Alongi, 1972; Finger & Frommer, 1968; Gabriel, Freer, & Finger, 1979) or an inclined plane discrimination (Thompson, 1982a) problem.

2. A sequence mixed with single- and double-alternation runs (or double-alternation runs only) has routinely been used in my laboratory for the purpose of reducing the frequency and duration of position habits. Evidence that criterial performance is not dependent upon the use of such spatial sequences has been presented earlier (Thompson, Lukaszewska, Schweigerdt, & McNew, 1967).

3. Since the central lateral nucleus was almost invariably invaded in those rats receiving VL, LD, and/or LP damage, the

possibility that this intralaminar nucleus is implicated in visual discrimination learning cannot be ignored.

4. The six structures found not to be implicated in original and/or reversal learning of a position habit include the amygdaloid complex, the zona incerta, the ventrobasal thalamus, the nucleus posterior thalami, the superior colliculus, and the dorso-medial midbrain reticular formation (Thompson, Note 1).

5. John (1967, 1972) views endogenous influences as readouts of specific memories. The anticipatory set would certainly represent a specific memory. More importantly, the presence of endogenous influences in widely dispersed regions of the brain may reflect the mobilization of excitatory and inhibitory processes attending the activation of an anticipatory set.

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ERRATUM

Moore, J. W., & Stickney, K. J. Goal tracking in attentional-associative networks: Spatial learning and the hippocampus. *Physiological Psychology*, 1982, Vol. 10 (2), 202-208—On page 204, the italicized word on line 21 of column 1, *association*, should be *antiassociation*. On page 207, the word "unchained" on line 27 of column 1 should be "unchanged."